Remarks/Arguments

The specification has been amended to ensure full compliance with the sequence rules set forth in 37 C.F.R. 1.821(a)(1) and (a)(2). Claims 1-3, 8 and 11 are pending in this application. Claims 1 and 8 have been amended. The amendments are of formal nature, are fully supported by the specification as originally filed, and should not raise any issues on new matter introduction. All claims amendments were made without prejudice and without acquiescing in any of the rejections or the reasoning underlying the rejections. Applicants specifically reserve the right to pursue any deleted subject matter in one or more continuing applications.

Sequence Rule

The specification has been objected to as allegedly failing to comply with the requirements of 37 C.F.R. 1.821(a)(1) and (a)(2) in that some sequences recited in the specification were not accompanied by sequence identification numbers. The Examiner specifically referred to the peptides TIP and TIP 12/1 recited in the legend of Figure 1 on page 5.

The foregoing amendments to the specification are believed to obviate this rejection. Applicants note, however, that the Examiner's reference to the legend of Figure 1 is in error, since it has already been supplemented with the required SEQ ID NOs in the amendment dated September 30, 2003.

Rejection under 35 U.S.C. 112, first paragraph, new matter

Claim 8 was rejected as allegedly containing new matter in its recitation that the agent which has the property of competing with mdm2 for binding p53 "does not inhibit the ability of p53 to induce cell cycle arrest or apoptosis in cells after DNA damage." The Examiner noted that the specification discloses support for "competing with mdm2 for binding p53, but does not inhibit the biological activity of p53."

Without acquiescing in the Examiner's position, and merely to expedite prosecution, claim 8 has been amended by deleting the phrase objected to, and replacing it with the language for which the Examiner acknowledged support in the specification. Accordingly, the Examiner is respectfully requested to withdraw the present rejection.

Rejection under 35 U.S.C. 112, first paragraph - enablement

(1) Claims 1-3, 8, and 11 were rejected for alleged lack of enablement. The Examiner acknowledged that the specification is enabling for an in vitro method for increasing the level of p53 protein in breast cancer cells that do not overexpress mdm2 by administering a peptide consisting of SEQ ID NO: 3, inserted in thioredoxin, but held that it did not reasonably provide enablement for an in vitro method for inducing growth inhibition or apoptosis in a population of "cancer cells in which mdm2 is not overexpressed," using an agent comprising a peptide, less than 25 amino acids in length, and including the peptide motif FXaaXaaXaaW (SEQ ID NO: 4)."

The rejection raises two separate but related issues of enablement: (1) the scope of the peptides used in the claimed methods; and (2) the scope of the cancer cells targeted by the claimed methods. As a result of the present amendments, the claims are now directed to disrupting the binding of p53 and mdm2 or inhibiting the production of mdm2, accordingly, the issue of the scope of cancer cells is moot. The question whether the use of the peptides of less than 25 amino acids in length, and including the peptide motif FXaaXaaXaaW (SEQ ID NO: 4) is enabled will be examined in the context of the new claim language. It is emphasized, however, that the deletion of the earlier reference of inducing growth inhibition or apoptosis of cancer cells no way implies that Applicants are in agreement with the Examiner's views, rather was made purely as a way of furthering the prosecution of the present application.

Applicants submit that the claims pending in this application are fully enabled.

The enablement requirement is whether or not a person skilled in the art can work the invention across the whole scope of the claim using the teaching of the specification and general knowledge without undue burden. There seems to be no debate as to whether one skilled in the art could produce all peptides falling within the definition provided in the claims without undue experimentation. Instead, the question is whether one of ordinary skill would reasonably assume that the peptides within the scope of the claim will achieve the purpose of the method, namely, disruption of the binding of p53 and mdm2 or inhibition of the production of mdm2.

In the rejection, the Examiner appears to focus on the fact that the specification describes some peptides that are better than others, noting, for example, that the specification teaches that TIP is 10 times less potent than TIP 12/1 in its ability to inhibit the interaction between p53 and mdm2, and that this has to be attributed to the 50 times less potency achieved by the wild-type peptide when compared with the peptide 12/1 in an in vitro competition assay.

Applicants submit that the fact that some peptides within the scope of the claims might be more potent than others is not sufficient to establish a *prima facie* case of lack of enablement. With regard to the definition of the peptides comprising SEQ ID NO: 4, the Examiner cites the results provided in the specification along with data and commentary provided in Bottger V et al (Oncogene, 1996, 13:2141-2147) to argue that the inhibitory strength of the peptide is crucial in order to induce growth inhibition or apoptosis in a cell. As noted above, the Examiner refers to the results provided for TIP 12/1 and wt TIP (see Table 1 and page 25 of the specification) to argue that peptides falling within the definition provided in claim 1 will inhibit the interaction between p53 and mdm2 to varying degrees and some may not be strong enough to achieve growth inhibition or apoptosis in the cell. It is certainly true that there will be variations in inhibitory strength. However, this does not support the Examiner's view that "it is unpredictable that a peptide of less than 25 amino acids in length, and comprising the motif FXaaXaaXaaW (SEQ ID NO: 4), wherein Xaa is any amino acid, could adequately increase the p53 activity, and consequently growth inhibition or apoptosis in a cancer cell in which mdm2 is not overexpressed."

The Examiner cited the following reasons as support:

1. Bottger et al. teach that specific activity of various synthetic peptide, having the common motif "FXaaXaaXaaW" as inhibitors of the hdm2-p53 interaction varies over 100 fold range.

2. Bottger et al. teach that the motif PXFXDYWXXL is the most potent inhibitor wherein each of the selected consensus residues is important for the maximum strength of interaction with hdm2.

3. Bottger et al. teach that the L of the p53 sequence TFSDLW is important for hdm2 and that tyrosine (Y) selected over the wild-type L in phage display increases the inhibitory activity, probably as additional binding points for hdm2, for improved stability of the peptide or its better conformational fit into the hdm2 binding pocket.

On page 8 of the Office Action, the Examiner states that owing to the above reasons, it is not possible to predict that peptides having the general formula FXaaXaaXaaW, including the wt p53 peptide of SEQ ID NO: 2, would have adequate strength of interaction with hdm2 to displace adequate numbers of the wild-type full-length, endogenous p53 from binding to hdm2, such that the activity of p53 is adequately induced, resulting in growth inhibition or apoptosis.

The first thing is to say that none of the above is evidence that would establish that it is more likely than not that a peptide having the general formula FXaaXaaXaaW would not achieve growth inhibition or apoptosis in a cell. The statements cited by the Examiner merely illustrate that some peptides are likely to be better than others.

Furthermore, the claims as currently amended no longer recite either growth inhibition or apoptosis of a tumor cell. It is therefore even more clear that the claims are enabled, since the Examiner gave not reasons and cited no evidence to show that the peptides within the full scope of the claims would not be expected to have the ability to disrupt the binding of p53 and mdm2 or inhibit the production of mdm2. While there are likely to be differences in the degree of this ability, such difference is not relevant to the issue of enablement. It is well established that the claims need not be limited to the best mode in order to meet the enablement requirement.

Additionally, and still on the question of enablement, the Examiner has further argued that the claim is not enabled for peptides being less than 10 amino acids in length. In support of this position, the Examiner advances that (a) Bottger et al. reports not being able to find an mdm2 binding phage from a hexapeptide library and that hexapeptides cannot provide sufficient correctly spaced contact points to bind the mdm2 binding pocket with high enough affinity; and (b) peptides having less than 10 amino acids would not contain the P at position 1 and the L at position 10 which the Examiner believes are necessary for providing strength of interaction.

In response, Applicants emphasize that the claims are not directed to the agents per se, rather are drawn to methods in which the agents used are characterized by a combination of structural and functional features. In particular, the claimed methods are performed by using agents which (1) comprise a peptide, less than 25 amino acids in length, and including the peptide motif FXaaXaaXaaW (SEQ ID NO: 4), where Xaa is any amino acid, and (2) have the property of disrupting the binding of p53 and mdm2 or inhibiting the production of mdm2. Accordingly, the use of agents which do not have the property of disrupting the binding of p53 and mdm2 or inhibiting the production of mdm2 is not within the scope of the claims. While it is true that the identification of agents of the specified structure which additionally has the specified biological property might require some experimentation, such experimentation is merely routine and not undue.

In the entire rejection, the Examiner appears to be unduly concerned that the claimed might include inoperative species. As set forth in Atlas Power Company v. DuPont de Nemours & Co., 750 F.2d 1569, 1576-77, 224 USPQ 409, 414 (Fed. Cir. 1984):

> Even if some of the claimed combinations were inoperative, the claims are not necessarily invalid. "It is not a function of a claim to specifically exclude . . . possible inoperative substances . . . " In re Dinh-Nguyen, 492 F.2d 856, 859, 181 USPQ 46, 48 (CCPA 1974) (emphasis and further citations omitted).. . . Of course if the number of inoperative combinations becomes significant, and in effect forces one of ordinary skill in the art to experiment unduly in order to practice the claimed invention, the claims might indeed be invalid. See e.g., In re Cook, 439 F.2d 730, 735, 169 USPQ 298, 302 (CCPA 1971).

However, the Examiner has not provided evidence necessary to establish that undue experimentation would be required to practice the invention. The law is clear that even extensive experimentation is allowed, if it is merely routine.

Applicants, again, refer to granted U.S. patents that are equivalent to WO 93/20238 and WO 96/02642, at least one of which (U.S. Patent No. 6,153,391) includes claims to methods that involve generically defined compounds (even including small molecules) that bind to MDM2 and interfere with its binding to p53. While Applicants appreciate that each case is examined on

its own merits, examination cannot entirely disregard the results of the examination of applications of similar disclosure of a closely related field.

For the reasons set forth above, the Examiner is respectfully requested to reconsider and withdraw the present rejection.

(2) According to the Office Action, even if Applicants overcame the above rejection under 35 U.S.C. 112, first paragraph, claims 3 and 11 would still remain rejected for alleged lack of enablement, for their recitation of a "portion" of p53 that is necessary for mdm2 binding or "at least 70% amino acid sequence identity."

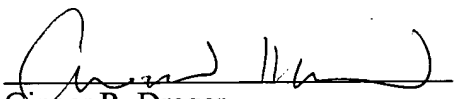
This rejection is legally incorrect. Claims 3 and 11 are dependent claims, depending from claim 1 and carrying its limitations. Accordingly, if claim 1 is enabled, as Applicants submit it is, claims 3 and 11, which are narrower in scope setting further requirements, are also enabled. Accordingly, the reconsideration and withdrawal of this rejection would be in order.

All claims pending in this application are believed to be in *prima facie* condition for allowance, and an early issuance of a Notice of Allowance is respectfully solicited.

Please charge any additional fees, including fees for additional extension of time, or credit overpayment to Deposit Account No. **08-1641** (Attorney's Docket No. **39749-0001APC**).

Respectfully submitted,

Date: August 22, 2005



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